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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,230	08/14/2001	Stanley B. Prusiner	06510056US4	6626

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BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,230	PRUSINER, STANLEY B.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,18,19,29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,18,19,29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed March 15, 2004 (hereinafter referred to as "the response") has been entered. Claims 1, 2, and 33 have been amended. Claims 11, 20-28, 30, and 34 have been cancelled.

Accordingly, Claims 1-10, 18, 19, 29, and 31-33 remain pending in the instant application.

Upon further consideration, the following grounds of rejection apply to the pending claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 29, and 31-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-18 of U.S. Patent No. 6,020,537. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims read on the claims of the issued patent (or are obvious over the claims of the issued patent).

Claim 1 is anticipated by Claims 7, 8, and 13 of USPN 6,020,537. In other words, Claim 7 of the issued patent falls entirely within the scope of Claim 1 of the instant application.

Claim 2 is obvious over Claim 2 of USPN 6,020,537 and any one of Claims 7, 8, or 13 of USPN 6,020,537.

Claim 3 is anticipated by Claims 7, 8, and 13 of USPN 6,020,537.

Claim 4 is anticipated by Claim 8 of USPN 6,020,537.

Claim 5 is anticipated by Claim 7 of USPN 6,020,537.

Claim 6 is anticipated by Claim 8 of USPN 6,020,537.

Claim 7 is obvious over Claims 9 and 10 of USPN 6,020,537.

Claim 8 is anticipated by Claim 13 of USPN 6,020,537.

Claim 9 is anticipated by Claim 13 of USPN 6,020,537.

Claim 10 is anticipated by Claim 13 of USPN 6,020,537.

Claim 29 is anticipated by Claims 7, 8, and 13 of USPN 6,020,537.

Claim 31 is anticipated by Claims 7, 8, and 13 of USPN 6,020,537.

Claim 32 is anticipated by Claims 7 and 13 of USPN 6,020,537.

Claim 33 is anticipated by Claims 7 and 13 of USPN 6,020,537.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 18, 19, 29, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a prion preparation comprising prions obtained from the brain of a transgenic mouse comprising a genome wherein an exogenous human, bovine, or sheep PrP transgene is

operatively inserted, and wherein the preparation comprises infectious prions (a) which infect and cause disease in an animal chosen from a human, a cow, and a sheep, (b) which are prions of a known strain, (c) the prions are present in a known number of infectious units, and further wherein the carrier is different from brain tissue of the animal chosen from a human, a cow and a sheep, does not reasonably provide enablement for a prion preparation comprising prions obtained from the brain of a transgenic mouse, wherein the transgenic mouse comprises any genetic modification that renders it susceptible to infection by a human, bovine, or sheep prion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a standardized prion preparation comprising prions obtained from a plurality of transgenic mouse brains and a carrier, wherein the preparation comprises prions (a) which infect and cause disease in an animal chosen from a human, a cow, and a sheep, (b) which are prions of a known strain, (c) are present in a known number of infectious units, and further wherein the carrier is different from brain tissue of the animal chosen from a human, a cow, and a sheep.

The specification reveals on pages 25-26 that the DNA sequences of the human, sheep, and cow PrP genes have been determined.

The specification fails to provide an enabling disclosure for the claimed prion preparation because the specification does not teach how to propagate prions from one species of animal, i.e. a human, bovine, or sheep, in a transgenic mouse other than in the brain of the transgenic mouse of the type described in the specification wherein both alleles of the endogenous murine PrP gene are ablated and an exogenous mammalian PrP transgene is operatively inserted. The claims encompass prion preparations isolated from any transgenic mouse having any genetic modification that renders it susceptible to infection by a human, bovine, or sheep prion, but the specification only teaches how to used transgenic mice having a specific type of genetic modification, wherein both alleles of the endogenous murine PrP

gene are ablated and an exogenous mammalian PrP transgene is operatively inserted. The specification does not teach how to obtain human, bovine, or sheep prions appropriate for the claimed preparation (where the carrier is different from brain tissue of the animal chosen from a human, a cow, and a sheep) from anything other than transgenic mice of the type indicated above. Accordingly, the specification does not teach how to propagate human, cow, or sheep prions in any type of transgenic mouse other than a transgenic mouse of the genotype Tg(HuPrP)/Prnp$^{0/0}$, Tg(BovPrP)/Prnp$^{0/0}$, and Tg(ShePrP)/Prnp$^{0/0}$, respectively. The claims encompass human, cow, and sheep prion preparations obtained from the brain of a transgenic mouse, wherein the human, cow, and sheep prions were propagated in the brain of a transgenic mouse having any genetic modification that renders it susceptible to infection with a human, cow, or sheep prion, but the specification does not teach how to accomplish this in anything other than the transgenic mouse of the type indicated above.

Accordingly, the specification fails to provide an enabling disclosure for the preparation of a broad scope of transgenic mice appropriate for the propagation and isolation of exogenous prions because the phenotype of a transgenic mouse cannot be predicted. While the specification discloses transgenic mice wherein both alleles of the endogenous PrP gene have been ablated and an exogenous PrP gene is introduced into the genome, and wherein the mice exhibit an enhanced susceptibility to infection by a prion from a divergent source when compared to non-transgenic mice, the phenotype of any other transgenic mouse harboring a different type of transgene construct cannot be predicted. The specification does not teach what phenotype would be expected in a transgenic mouse, other than a mouse of the type disclosed in the specification. No guidance is provided with respect to how one would have prepared any other type of transgenic mouse exhibiting a transgene-dependent phenotypic alteration which renders it susceptible to infection by a human, cow, or sheep prion. The mere capability to perform gene transfer in a mouse is not enabling for the requisite transgenic mice because the desired phenotype cannot be predictably achieved simply by introducing transgene constructs of interest into the genome of a mouse.

While gene transfer techniques are well-developed for a number of species, especially the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic mouse depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression are not readily understood. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). With the limited working examples, the production of an appropriate phenotypic alteration (i.e. one that renders the mouse susceptible to infection with a human, cow, or sheep prion) resulting from the introduction of a genetic modification other than that disclosed in the specification (i.e. introduction of an exogenous PrP gene in conjuction with an ablation of both alleles of the endogenous PrP gene), is highly unpredictable.

The specification fails to provide an enabling disclosure for the preparation of the broad scope of transgenic mice covered by the claims because the species barrier, discussed in U.S. Patent No. 5,792,901 (column 14, lines 1-10), makes it difficult to predict whether introduction of a specific PrP transgene (of any species origin) into a host mouse will render the host susceptible to infection with prions obtained from the species that is the source of the exogenously introduced PrP transgene. For example, it is not readily apparent that a mouse harboring a human PrP transgene while also retaining its own endogenous PrP gene would be susceptible to infection with a human prion. Thus, the specification does not teach

how to make a transgenic mouse that is susceptible to infection with a human prion in the absence of ablation of both alleles of the endogenous mouse PrP gene.

The specification fails to provide an enabling disclosure for the claimed prion preparations obtained from a transgenic mouse with an exogenous PrP transgene and with a single endogenous PrP allele ablated or with neither allele ablated because the specification teaches that when transgenic mice are made in accordance with the invention, both alleles of the endogenous PrP gene must be ablated in order for the mice to become susceptible to infection with a prion from the species that is the source of the exogenous PrP gene (see, e.g., column 31, Example 8 of U.S. Patent No. 5,792,901). For example, Tg(HuPrP) mice are resistant to infection with human prions.

With regard to Claim 9, the specification fails to provide an enabling disclosure for obtaining prions from Tg(HuPrP), Tg(HuPrP)/Prnp$^{+/0}$, Tg(HuPrP^{CJD}), Tg(HuPrP^{CJD})/Prnp$^{+/0}$, Tg(ShePrP), Tg(ShePrP)/Prnp$^{+/0}$, Tg(BovPrP), Tg(BovPrP)/Prnp$^{+/0}$ mice for the reasons discussed in the preceding paragraph.

The specification fails to provide an enabling disclosure for the claimed prion protein standard for the reasons discussed above regarding the scope of enablement of the transgenic mice that are appropriate for the isolation of exogenous prions.

The specification fails to provide an enabling disclosure for the claimed prion protein standard comprising exogenous prions isolated from any transgenic mouse produced by any genetic manipulation that permits infection by exogenous prions because the specification does not disclose any method for rendering a mouse susceptible to infection by exogenous prions other than by ablating both alleles of the endogenous murine PrP gene and inserting an exogenous PrP gene derived from another species of animal. The claims encompass any genetic manipulation that renders the mouse susceptible to infection by exogenous prions, but the specification is enabling for only one genetic strategy to produce susceptible mice. Furthermore, as discussed above, the phenotype of a transgenic mouse cannot be predicted.

Given the limited guidance in the specification, the limited working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use appropriate transgenic mice having a genetic modification other than that disclosed in the instant specification. Thus, the skilled artisan would have been required to engage in undue experimentation in order to make the full scope of the claimed prion preparations.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER